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Cannabis, the Plant of the Unlimited Possibilities

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Authors' contributions

This work was carried out in collaboration between both authors. Author DEK wrote the first draft of the manuscript. Author KD wrote the final draft and approved the final manuscript. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

This review paper gives an overview of *Cannabis Sativa*, also known as hemp, which has been cultivated and used century's B.C. due to its medical, hallucinogenic and agricultural properties. Cannabis has been described in 1938 as the billion-dollar plant but has lost its value in the U.S. due to regulatory and legislative issues.

Hemp has seen as new push In the U.S. with the introduction of the 2018 Farm Bill which allows on a federal level to grow hemp, pending on individual state regulations. Currently, industrial hemp production is allowed in at least 38 U.S. States under strict regulations.

Today hemp is used in counties that do not have as strict regulations as the U.S. in a variety of applications such as beauty products, carpets, cooking oil, personal care products and textiles.

Hemp can be considered as an alternative feedstock due to its low lignin and high cellulose level for biofuel application as an alternative to replace petroleum-based fuels and gases.

In the U.S. hemp research in these areas has stalled due to the complexity of the law.

Beside industrial application such as ropes, textiles, shoes, etc., hemp today is used in pharmaceutical and medical applications, by extracting Δ9-tetrahydrocannabinol and cannabinoids from the leaves and fluorescence of the hemp plant that contain no more than of up to 0.3% of these compounds. The use of hemp plants with higher levels are strictly forbidden in most countries.

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Several extraction processes of cannabinoids from hemp are used They all use a solvent for extraction but differ in terms of efficiency, usage range and other factors influencing the extraction. Nonetheless, overconsumption of cannabis products can be associated with several side effects, that can cause serious physiological and psychological damage in the human body may cause serious damage.

Keywords: Wood flour; additive; papermaking; hand-sheets; paper properties.

1. INTRODUCTION

Described as the new billion-dollar plant in 1938 by the Popular Mechanics magazine [1] and still one of the most controversial plants, even today [2]. Industrial Hemp or more precisely Cannabis is a C3 plant and therefore categorized in the family of *Cannabaceae* [3]. Cannabis has been already cultivated and used centuries B.C. due to its medical, hallucinogenic and agricultural properties, Cannabis has become a loathsome but also beloved plant. Cannabis including high levels of delta-nine tetra hydro cannabinol (Δ9-THC) has inebriant effects on the human body. Thus, physiological effects, including changes in the heart and respiratory rate, altered blood pressure, dry mouth and increased appetite, but also feeling of euphoria, altered time perception, lack of concentration and aggrieved learning can be caused by drug abuse from Cannabis [5]. However, Hemp is not a drug in particular. Whether a specific growth is specified as a drug type or fibre type, depends on the level of Δ9-tetrahydrocannabinol (Δ9-THC). Fig. 2. Shows the varieties of cannabis. Cannabis can be distinguished in *C. sativa* (a fibre type), *C. indica* (drug type containing levels of Δ9-THC, higher than 0,3%), and *C. ruderalis* (Janish, intermediate characteristics) [6].

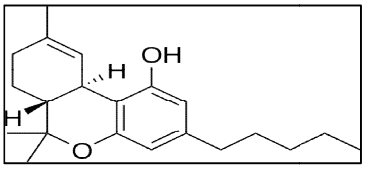

Fig. 1. Δ9-tetrahydrocannabinol (Δ9-THC), [4]

Industrial Hemp developed to be one of the top crops not only today but also in the history of agriculture. It is one of the oldest annual crops with multi-purpose cultivation for a wide variety of products such as hemp stem cellulose and fibre for paper and textile, hemp seed oil (CBD), food, cosmetics and pharmaceutical industries [9,10]. Withal *Cannabis Sativa* is part of modern medicine. Multiple therapeutic but also expedient medicinal properties such as analgesic, antibacterial, antidiabetic, antiemetic, antiepileptic, anti-inflammatory, antiproliferative, antipsychotic, antispasmodic, is given by the plant. Further posttraumatic stress disorder, anxiety and schizophrenia can be effectively threatened [9,11]. Nonetheless, cultivating or consuming cannabis as a drug, having high levels of delta-nine tetrahydrocannabinol (Δ9-THC) is strictly forbidden in most countries. Cultivating industrial Hemp [*Cannabis Sativa L.*], accumulating less than 0.2–0.3% of Δ9-THC but with higher levels of Cannabidiol [CBD] and has, therefore, no intoxicating effects on the human body, finds its use in the agricultural industry worldwide and is officially allowed in Canada, and USA and many European countries [1,3]. In the US the 2018 Farm Bill allows on a federal level to grow hemp, pending on state regulations [12]. Currently, industrial hemp production is allowed in at least 38 US States but requires to the grower to be registered under a program that requires testing and inspection with the state and/or federal government [13].

Brought to America in 1619 for applications and the textile industry [14], Industrial Hemp is certainly used for merchandise products nowadays. The most popular products on the market are those containing CBD. Products containing CBD are either beauty products, such as tinctures, masks and gels or medical products such as transdermal delivery systems [15]. For obtaining any tincture, tea, gel or miscellaneous other products, tetrahydrocannabinolic acid (THCA) and Cannabidiolic acid (CBDA) have to be extracted and brought to their decarboxylated form THC or CBD [16], thus several procedures have been developed. On the one hand, boiling water can be used to prepare a tea from dry plant material. On the other hand, to obtain reasonable concentrated tinctures and teas, organic solvents such as ethanol are much more effective [17,18]. Incidentally, ethanolic tinctures have a long history not only in the United States but also in other countries such as Great Britain and Germany. By heating, either the plant material or the final product tinctures are made. However, since too many chemical constitutions

are being removed by the ethanolic extraction, ethanol as an extraction solvent is not as good as other organic agents. For more refined extracts other organic solvents such as Chloroform or Hexane can be utilized. Since compressed gases are available, highly concentrated preparations can be produced, but therefore explosions and fires, causing deadly accidents, are much more likely to happen. Much safer is the supercritical extraction through compressed liquid CO_2, with which pure final products are obtained. Nonetheless, heating is required during the process to decarboxylate all the acid forms to their analogues. Further, there is the latest research about microwave-assisted extraction of cannabinoids from Hemp [9,14,17, 19].

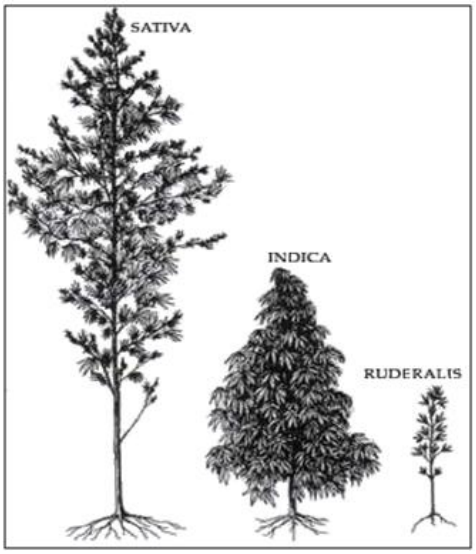

Fig. 2. Variety of cannabis, *sativa* (left) industrial fibre type, *indica* (middle) drug type, *ruderalis* intermediate characteristics [7]

Nowadays, finding sustainable energy resources is one of the top priorities. Since not only the demand for energy has increased drastically but also global energy resources are under enormous pressure due to overexploiting. Industrial hemp might be therefore one of the top solutions since energy can be produced through biomass production. [17,20-22]. Due to the high biogas yield (3066 m^3 /ha), which is in the upper range of many other plant straws such as clover grass (2900-4000 m^3/ha), industrial hemp is a fairly good opportunity for long term biogas production. As industrial hemp produces the same amounts of methane yield/ha but has higher carbohydrate contents and lower amounts of lignin, it has great values which make it ideal for methane production [6,17]. Nonetheless, biogas production via industrial hemp is not well investigated and has not got any considerable attention so far.

Fig. 3. Industrial hemp variety of cannabis, *sativa* [8]

Unfortunately, there is also no compact assemblage about Cannabis, respectively Hemp, marihuana and all its potentials in the agriculture, industry in general, medicine and everything that comes with it. Therefore, this review aimed to compile a collection of the utmost important facts about this theme, with the result that scientific impressions can easily be gained about whatever, the interest of Cannabis one, no matter if expert or layman, may have.

2. NATURAL COMPOUNDS OF HEMP

From *Cannabis Sativa* more than 750 natural compounds of different chemical classes can be produced [23]. The largest chemical class includes 140 terpenes [24]. Cannabinoids as one of the most important compounds are classified in one class composed of 86 terpene phenolic secondary metabolites [25]. Other compound classes include 50 identified hydrocarbons, 34 sugars and related compounds, 27 nitrogenous compounds, 25 noncannabinoid phenols, 23 fatty acids, 23 flavonoids, 20 simple acids, 13 simple ketones, 13 simple esters and lactones, 12 simple aldehydes, 11 proteins, 11 steroids, 9 elements, 3 vitamins, and 2 pigments [24,26-30].

3. LEGISLATION AND CURRENT USE OF CANABIS IN THE USA AND EUROPE

Europe has already recognized the potential of Cannabis for the industry. CBD containing

products are available in in a large variety in almost every grocery store. Primary the cosmetic industry benefits a lot from the rising demand on CBD containing crèmes, tinctures and other alike products. For that reason, modern hemp is selectively bred and currently, 51 hemp cultivars have been approved for industrial purposes by the European Union [6].

The richness of cellulose makes hemp ideal for biofuel production [31,32], dense flowering varieties offer abundant seed or high CBD to THC ratios, its fibres are used for pulping and as fine fibres for textile products [33-35].

In most European countries, cultivars with a THC level of under 0.3% are allowed for fibre, seed and cannabidiol production [36]. Whereas Italy only allows cultivars with a THC level under 0.2% [37].

In the US industrial hemp production of *Cannabis sativia L.* and any derivate with a THC level of not more than 0.3% on a dry weight, basis is guided by the 2018 Farm Bill that removes industrial hemp from the Controlled Substance Act and allows growing and cultivation for agricultural use of hemp as research and pilot program in States where the production of industrial hemp is legal under state law. However, legal requirements for growing and cultivating hemp under a pilot and research program are very complicated and strict enforced [38,39]. At present time cultivation of industrial hemp is not legalized in the State of Idaho, South Dakota, Mississippi, District of Columbia, as well las the 5 US territories American Samoa, Guam, Northern Mariana Islands, Puerto Ricco and the U.S. Virgin Islands [38].

4. MARIHUANA VERSUS HEMP

Marihuana and Hemp are like the Asterix and Obelix from the famous comic-series *Astérix* by René Goscinny and Albert Uderzo in 1959 [40, 41].

They are both originally from the same sort of plant*, Cannabis Sativa L*. and still, they are almost completely different from one another, since they have umpteen chemical compositions. Besides, their outer looking is different, so as their field of use [42].

For medical uses, there is a primary interest in the Cannabinoids of Cannabis. The most important two cannabinoids are the decarboxylated forms of THCA [THC-acid] delta-nine tetra hydro cannabinol [Δ9-THC] and cannabidiolic acid [CBDA]. Those Cannabinoids are obtained by different extraction processes [43]. Used for the extraction is most commonly only the fluorescence. Marihuana is, therefore, the ideal choice, since it grows low, has thin stems, but also a lot of branches and leaves and most importantly a massive and heavy florescence. Further, Marihuana needs special cultivation technics, each plant needs due to its high amount of branches a lot space to grow and it is also highly sensitive in terms of light and humidity. Due to its high levels of Δ9-THC] and CBD, Marihuana is not only ideal for medical application but also as a drug. THC has intoxicant effects on the human body and is responsible for the so-called "high" feeling. Male plants are not used in the cultivation of marihuana, since they do not have blossoms and might also pollinate the female plants. This can result in immense crop losses since the fluorescence will be useless if it is filled with seams.

In contrast to Marihuana, hemp has lower levels of delta-nine tetra hydro cannabinol but higher levels of terpenes. Further, the plant has thick stems, much fewer branches and leaves and a smaller florescence. Thus, hemp is much easier to cultivate and does not need special treatments, such as a lot of space to grow, the right level of humidity or temperature.

This easiness makes the plant especially valuable for the agricultural and fibre type industry. Fibre type products such as paper, fabrics and any further fabric products and even plastic can be produced with industrial Hemp. Further Hemp has an extremely high growth rate from 50 centimetres per month and grows up to an elevation of five meters [21]. Thus, industrial hemp is a perfect resource for a large number of sustainable application areas. Due to the high availability of mass, as a result of the high growth rate and the thickness of the stems, industrial hemp presents itself beneficial for biomass production. There is even research about the potential capability of biogas production with the residues of special industrial hemp which was used for CBD-OIL production.

Industrial hemp is considered ecologically friendly and sometimes even used for soil regeneration in highly contaminated areas, it is a considerable resource for the agricultural industry and future sustainable energy production [44,45].

5. CANNABIS IN THE MODERN INDUSTRY

Cannabis is a versatile plant and one of the oldest annual crops with multi-purpose cultivation for a large pallet of products. On the on hand, Paper and textile production are possible due to hemp stem cellulose and fibre, on the other hand, hemp seed oil, which is obtained via either cold pressing, hydrocarbon solvent or through supercritical carbon dioxide fluid extraction. It is suited not only for the pharmaceutical industry, due to its many medicinal and therapeutic properties such as analgesic, antibacterial, antidiabetic, anti inflammatory, antispam, but also for the food and cosmetic industry [46].

5.1 Food Industry

Since products containing at least traces of cannabis have become more and more popular over the years, there is hardly a product genre in which one cannot find cannabis-related products.

The food industry benefits from the Cannabis hype. And as a matter of fact, Cannabis has various beneficial properties. It is a rich source of essential fatty acids and contains a unique and rare ratio of -6 linoleic and -3 α-linoleic acid (-6/ -3) as 3:1, which makes it an ideal product for vegetarian diets [6]. Further, it improves the immunity and cardiovascular health and is beneficial for hair, nails and skin tissues. Also, it is a tremendous source of protein, fatty acids, enzymes, terpenes, vitamins and insoluble fibre. This makes it beneficial for diabetic diets, metabolic process and low cholesterol and hormonal balance, due to its rare oil containing g-linolenic acid [6].

5.2 Consumables

Considering the different effects of Cannabis depending on the sort of plant, chemical composition, strength and homogeneity based on the raw plant material, containing either high or low levels of Δ9-THC, you have to differ between the consumables. Incidentally, there are products, which are only Cannabis-related or just have a placebo effect, such as chewing gums. Nonetheless, there are also cannabis products made for consumption, which have therapeutic or toxic effects on the human body. For that matter, the cannabinoids must be decarboxylated to their natural form via high temperature. This is not a problem when the food products are baked or heated at high temperature. Popsicles, soft drinks and any other product that is not subjected to high heat, has to contain plant material which has either been aged or heated before.

Nevertheless, a variety of different products entered the food market in the last decades. Primary, food products such as chewing gums, mints, chocolate etc., containing lower levels of CBD are gaining on interest in the international market. But also teas for medical treatment are more and more in use and gain in popularity. In addition, hemp oil can be purchased as a nutty-tasting salad dressing [1,20,37,45,47-51].

5.3 Cosmetic Industry

Not only the food and the medical industry benefits from the therapeutic properties of Cannabis. Cannabis also applies to cosmetics. The rare ratio of -6 linoleic and -3 α-linoleic acid (-6/ -3) as 3:1 is expedient for hair, nails and skin tissues [6]. Since not only teenagers but also grown-up men and women are fighting against acne, CBD oils, masks and other therapeutic products are a possible solution. Due to their antibacterial, anti-inflammatory, fumigating and scouring ability CBD products are ideally suited for cosmetic products, concerning skin issues. Further, cannabinoids are a group of active chemical compounds, which stimulate the viral balance in our body. They are both antiviral and antibacterial and studies already efficacy in the cure of chronic skin conditions such as eczema, acne and psoriasis. The antioxidants contained in the plant can also minimize premature signs of ageing [6].

For creating a crème, made for the cosmetic use, the CBD has to be mixed with oil. Most commonly used is hemp-oil, which is produced from cold-pressed hemp seams. In contrast, CBD oil is made out of the stems, fluorescence and leaves of the plant.

Nonetheless, it does not have to mix with hemp oil, necessarily. CBD can also be put together with olive oil or grapeseed oil for producing a functional and therapeutic crème [52]. Shampoos, lip balms, tinctures, masks, crèmes etc. are the most common beauty products.

5.4 Agricultural Industry

5.4.1 Brief history

Hemp is traditionally cultivated for its fibres but had therefore in the temperate climate low THC

levels. Further, was it already cultivated by the Egyptians for its therapeutic and medical properties.

Cannabis came to North America for the first time in the early 1600s. It played an important role in the Pennsylvanian agriculture during the 1700 and 1800 and was then grown in many parts of the country [14].

Back then, hemp was used for the production of oil, ropes, grain bags, Conestoga wagon covers and clothing and paper in many parts of the world [53,54].

Since marihuana hemp types with high THC levels were evolving, industrial hemp got linked to it. This led to legislation and lastly even to the Marihuana Tax Act of 1938, which made both hemp and marijuana controlled substances and effectively eliminated the production of industrial hemp with a few exceptions when fibre was needed during WWII [55].

Cannabis could not be distinguished into high or low levels of THC until 1960.

In 2014, Section 7606 of the Agricultural Act (the Farm bill) changed the legal status of Cannabis. Industrial hemp was now allowed to be grown for three different limited circumstances. by researchers at an institute of higher education, by state Departments of Agriculture, or by farmers participating in a research program permitted and overseen by a state Department of Agriculture [10].

By 2017 hemp cultivation was allowed in Pennsylvania on a research basis, but only under the supervision of the Pennsylvania Department of Agriculture. Since then the interest of commercial production of hemp has increased and Hemp is produced today in 38 U.S. states for the use of its fibres or research purposes [13]. Nevertheless, there are also some hemp growths for dual purpose. But this requires not only specialized harvesting machinery but also management.

Today hemp is used in a variety of industrial applications and its application ranges from consumer textiles for clothing and shoes to industrial products such as ropes, nets, carpet, tarps, and industrial products including paper, building materials, insulation materials, and concrete with hemp fibres for higher insulation values and insect resistance. Hemp is also used for animal bedding, bioenergy production, composting and mulch. Hemp oil is used as a food supplement, birdseed, personal care products such as soaps, beauty products and moisturizer. Hemp seeds are used in bakery goods, protein flour.

5.4.2 Hemp production

Hemp cultivation growth requires best to well-drained soil with a pH between 6.0 and 7.0. It does not grow well on wet soils or soils with heavy clay content. It is further sensitive to soil crusting and soil compaction and a short-day plant mean it requires less than twelve hours of sunlight.

The Penn State Agricultural Analytical Services has developed fertilizer recommendations for hemp. In soil with optimum levels of phosphorus (P) and potassium (K), recommendations for a crop with a 1,500-pound yield potential would be 150 pounds of nitrogen (N), 30 pounds of phosphate (P_2O_5), and 20 pounds of potash (K_2O) [9].

Just like forage crops, Hemp can be grown in a tilled seedbed, which is firm, level and relatively fine. Even though they have not been volubly in trials, Hemp is sensitive to be affected by diseases like grey mould (*Botrytis cinerea*), white mould (*Sclerotinia sclerotiorum*), bacterial leaf spots, viruses, and Pythium root rot and blight during establishment. Additionally, insect-like cutworm, grubs, flea beetles, grasshoppers, and aphids, Japanese beetle (only attracted to male plants as current trials show) or other animals such as Mourning doves or Slugs, are likely to destroy hemp plants, especially when harvesting is delayed. However, the destruction through woodchucks or deer is in contrast to other crops, slightly uncommon and not as fatal.

There are both long and short seasoned plants. The long-seasoned plants should be planted in May to early June. Short seasoned Canadian growths can also just be planted from mid to late June.

Industrial Hemp should be planted in a depth of ½ to ¾ inch. Depending on the variety, general planting rate from 25 to 35 pounds per acre are recommended for industrial Hemp. Further depending on the variety is the sort of planting. It can be either planted in rows, like corn. Then the cultivation requires some mechanical weed control since there are no herbicides established

on hemp so far. Further control offers no-till methods, which use burndown herbicides. It can also be planted like small grain, with a grain. "For fibre production, planting is best done in drilled stands at seeding rates of 35–50 pounds per acre, which should result in stands of around 15 plants per square foot [9].

5.4.3 Harvesting

The plants still being green, hemp is harvested for hempseeds when it begins to shatter. Nevertheless, about 70 per cent of seeds will be ripe at this time, and the moisture is about 22-30 per cent.

When hemp is cultivated for its fibre, the harvesting usually takes part between early bloom and seed set, depending on the quality of the fibre.

Due to the strength of the fibres in the stems harvesting with combine might cause problems as the fibres wrapping in the combine can cause damage.

After the hemp is cut, it must undergo a process called retting. The bonds between the two different types of fibres in the hemp plant, the bast (the outer long fibres) and the hurds (inner short fibres) are being severed.

The most common process for that matter of fact is called field retting and involves leaving the crop in the field for up to five weeks to allow a field decomposition process to occur. Windrows are raked two or three times before harvest to dry and remove leaf materials. Afterwards, the crop is dried and baled in round or square bales and ´hauled to a storage facility.

Before the plant material is manufactured into the final product, the bust and hurds are separated.

Cultivating Cannabis can have environmental impacts. Soil pollution, pollution of surface or groundwater or any other contaminations are possible, due to the handling of pesticides and other chemicals. Yet, Cannabis is an ecofriendly plant, and can even be utilized for soil regeneration in highly contaminated areas [44, 45].

6. DIFFERENT EXTRACTION PROCESSES FOR CANNABINOIDS

There are several extraction processes of Cannabinoids from Hemp. They all differ in terms of efficiency, usage range and other factors influencing the extraction.

For obtaining a high level of cannabinoids, usually dried fluorescence is utilized.

The harvested plant material is cleaned and dried and ground (or cut). Low particle size enhances efficiency.

Fig. 4. Examples of industrial products of cannabis: a) pain relive, b) dietary supplement, c) muscle balsam, d) & e) various hemp CBD gummies, f) & g) hemp seeds with and without husks, h) skincare, i) hemp flour, j) hemp protein, k) pressed hemp cooking oil [56]

6.1 Water Extraction

In comparison to the other extraction processes, the extraction of Cannabinoids through water is a rather primitive method. Nonetheless, Hazekamp et al. conducted a laboratory study about the potential of water used as an extraction agent. Therefore, one gram of dried plant material from a chemotype legally cannabis plant grown in the Netherlands, was put into boiled water for 15 minutes. Afterwards, the leftover solids were removed. Some samples of the tea were reconstituted in ethanol, after lyophilized (freeze-dried) to complete dryness, and analyzed using a validated HPLC method. Further analytics showed also that longer boiling periods, in this case, double the time 30 minutes, doubled the concentration of Δ9-THC but it did not result in complete conversion from Δ9-THCA to Δ9-THC and therefore an increase in the level of Δ9-THCA.

The plant material had a Δ9-THCA content of 191 mg/g (19.1%), Δ9-THC content of 6 mg/g (0.6%) and a total amount of Δ9-THC in one gram of blossoms amounted to almost 200 mg. Incidentally, the tea (one Liter volume) contained only about 43 mg of Δ9-THCA and only 10 mg of Δ9-THC.

Reasonable for that low concentration is the solubility and saturation of the water phase with the lipophilic chemicals, which is strongly circumscribed [17].

6.2 Ethanol Extraction

Organic solvents are much better solvents to extract cannabinoids and prepare highly concentrated extracts and tinctures.

To alleviate the transformation of the biosynthetic acids' forms into their neutral forms it is utterly important to heat the plant material or the final product or treat it otherwise. The process is utterly successful with hot ethanol, typically increased to approximately 60°C. The ethanol is circulated to the plant material. After 24 hours of recirculation, the ethanol is replaced by fresh ethanol. In this way, all of Δ9-THCA, Δ9-THC, and other cannabinoids can be extracted.

However, ethanol is not selective since many other chemical solvents are also removed. Further, the placebo plant material may burn more rapidly and differs considerably in its organoleptic properties from none extracted material [17].

Ethanol is also used as a co-solvent since it can extract high polarity cannabinoids.

6.3 Supercritical Fluid Extraction with CO_2 (SFE)

While other organic solvents, such as hexane, chloroform or butane are well functional for extracting high amounts of Cannabinoids, but however dangerous, since they are either toxic (hexane and chloroform) or they are easily flammable and can lead to explosions and therefore serious injuries, the SFE- method is a much safer and inexpensive approach and the physiochemical properties of CO_2 are very well known. Still, there are risks from asphyxiation and high-pressure failures [12].

SFE has been proved as an easy green technology with high efficiency for extracting oils and a large variety of bioactive components from vegetable matrices and botanicas. Further, physicochemical properties of CO_2 Therefore, liquid CO_2 is increasingly employed for purification of phytocannabinoids [6,14.].

CO_2 reaches a supercritical state at 304.25 K and 7.39 MPa and returns to the gas state under ambient conditions. This allows a simple solute recover, providing a solvent-free product.

The solvent strength can be turned with changes in pressure and temperature.

Yet, CO_2 has a very low polarity. Modifiers, like co-solvents (ethanol, water, acids) can be utilized to overcome the low polarity. Also adding processes like Pressurized liquid extraction (PLE), Enzyme-assisted extraction (EAE) or HPLC (High-Performance Liquid Chromatography) help to modify and improve the procedure [6,14,18].

Laura J Rovetto and Niccolo V. Aieta describe the extraction procedure in a publication about Supercritical carbon dioxide extraction of cannabinoids from cannabis sativa L. [14] as in the following.

Two vessels of five litres are utilized for the process, both suitable for a series configuration with maximum pressure up to 60MPa.Also, there are three independently heated collecting vessels, or more precisely Cyclonic Separators (CS) of one litre, each provided with manual pressure control.

The pressure in the extraction vessels is regulated by an automatically actuated needle

valve acting as a Back-Pressure Regulator (ABPR). Further, the extraction vessel temperature is controlled by an electrical jacket.

500+-2 g of ground material is placed in an extraction vessel of five litres. The capacity of the extractors is about 1,7-2 kg of material. Therefore, the left space is filled with stainless steel wood and the plant material is packed in the central area of the extraction vessel.

CO_2 is cooled down to approximately 276 K to provide liquid state and proper density. After passing the high-pressure pump which delivers a maximum mass flow rate of 200 g/min, the solvent is heated to bring the liquid to supercritical state and reaches then the extraction vessel, in which plant material is pressurized with CO_2. [Depending on the experiment ethanol is mixed with the CO_2 mainstream via a co-solvent pump (mass flow up to 50 g/min) before reaching the high-pressure pump.

The supercritical stream dissolves the target components from the vegetable matrix and carries them from the extraction vessel the cyclonic separators for a controlled depressurization process. The separator conditions are setup at levels below the operating conditions used during the SFE to separate different fractions. The configuration induces a stepwise decrease of supercritical CO_2, so heavy, middleweight and light components can be separated from the supercritical solvent. The material is collected periodical during the SFE process. And the CO_2 gas is afterwards recirculated to the system [14].

6.4 Microwave-Assisted Extraction (MAE)

Even though there is hardly research about the extraction of cannabinoids with microwaves, it is still a good method for targeted extraction of Cannabinoids from hemp nuts with high efficiency. In comparison with other extraction processes, MAE achieves the highest extraction yields of total cannabinoids. Besides, substantial cell rupturing occurring in the microstructure of hemp nut, indicate improved dissolution of target compounds during the extraction process when using the MAE process. This makes the method a rapid, economical and environmentally friendly extraction method that is both effective and practical for industrial applications [19]. Incidentally, it is, just as with all other extraction processes, necessary to optimize the procedure, such as with compatible extraction processes like Response surface methodology (RSM) which is a statistical and mathematical technique for developing, improving, and optimizing the design process [58].

As the extraction process is only assisted by the use of microwaves, a suitable extraction solvent has to be applied. As researches from [19] show, Methanol with its good abilities in absorbing microwaves, being highly efficient in converting microwaves into heat, having a strong ability to dissolve the analytes of interest, being highly interactivity with the matrix, and being highly selectivity toward the analytes, and low selectivity toward unwanted matrix components seems to be the best solvent over Acetonitrile, Ethanol, Isopropanol, and Ethyl acetate. Even though, all listed solvents are utilizable.

6.5 Optimizing the Process

Factors like the temperature, the microwave power and the extraction time are withal likely to influence the yields of Cannabinoids [19].

Time is an important factor when extracting Cannabinoids with MAE. In contrast to other extraction processes, times at MAE are short. Long extraction times bring the risk of degradation of thermolabile components [19,47].

The microwave power can influence the time necessary to reach the set temperature during the extraction process, as well as the so-called "bumping" phenomenon. Lower power may avoid this phenomenon and generate a high-power output [50].

The temperature, as the most investigated parameter in MAE, is likely to influence the Cannabinoid extraction sustainable. Rising the temperature also raises the efficiency of the extraction. The temperature influences the desorption of analytes from the sample to the matrix. Besides, higher temperature improves sample wetting and matrix penetration by reducing the surface tension and solvent viscosity [59].

6.6 Further Assisting Extraction Processes

6.6.1. Pressurized Liquid Extraction (PLE)

PLE is a very promising bioactive compound extraction. During the process, the solvents are used near their supercritical region.

It is performed in an accelerated extraction apparatus. Different polarity solvents are used such as acetone, mixtures of Ethanol and water [6]. The solvent is maintained in the liquid state the whole process.

The process is based on pressures between 50 psi to 300 psi, temperatures between 50ºC to 200ºC and a processing period of 5 to 10 minutes [60].

6.6.2 Enzyme-Assisted Extraction (EAE)

The residues get suspended in sodium acetate buffer. Then, the cellulyticenzyme mixture Viscozyme® L is added to reach an enzyme/substrate (E/S) ratio of 6% v/w. Then it is incubated in a thermostatically controlled shaker. It is terminated by immersing the centrifugal bottle in a boiling water bath, followed by rapid cooling and centrifugation.

6.6.3 Soxhlet Process (SOX)

It is one of the most conventional and economical/user- friendly processes, which is used for hemp oil extraction [61].

The organic solvent, for example, n-hexane is heated to reflux and floods into a glass thimble. The Solid material accumulates in the thimble [6].

6.6.4 Percolation process (PER)

The material gets immersed in the solvent. Then, the solvent is reached through pores in ´to voids of the material. Thus, the oil gets extracted.

No study or literature is appearing for using PER for the extraction of Cannabinoids from Hemp [6].

6.6.5 Ultrasonication process (ULT)

Chemical and physical effects on the separation time reduce the extraction time. Ultras sonic frequencies over 20 KHz are used.

High-intensity soundwaves create pressure differences followed by volume expansion. Thus, voids between the material are filled by the solvent. High pressure further creates cavities due to the collapsing voids.

The UTS process is usually followed by ULT. UTS is the synthesis between ULT and SOX, to correspond to the maximum yield of ULT.

The STU process is further a SOX treated ULT [9].

7. CANNABIS AS A FUTURE BIOENERGY RESOURCE

The global energy demand is rising. Still, energy is one of the most important commodities of life in modern life and a secure and sustainable energy supply ensures socio-economic development of any country [62]. But fossil energy resources are already getting exploited to their maximum. Besides, their production is not economically friendly and will cause serious problems for humanity, when it not gradually stopped.

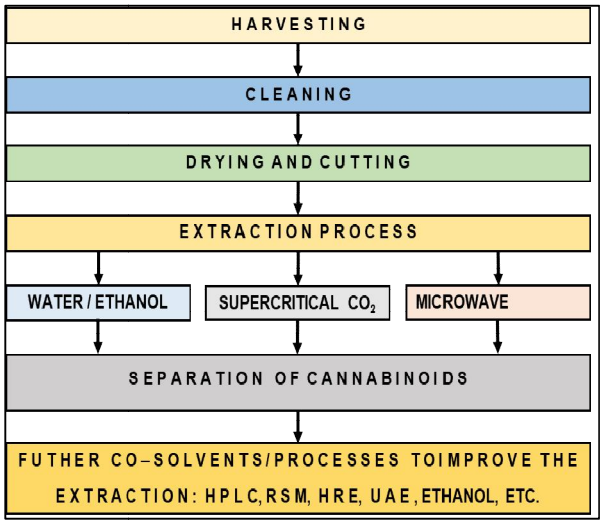

Fig. 5. CBD production process [57]

For that reason, potential renewable and sustainable energy resources must be found and investigated. Replacing fossil energy resources with economically friendly and reliable ones to cover the overdemand of energy should be the aim.

Since incorporating a sustainable bioenergy supply to the existing fuel system is one potential solution approach, biomass conversion into biofuels has gained a lot interest, and is not only an economically friendly but also a sustainable and renewable energy resource [63].

Biomass contains all kinds of organic waste like wood, sewage sludge from water treatment plants, household organic waste, industrial oil and greases, manure and certain crops. Biomass conversion to bioenergy can either occur through Gasification, digestion or combustion. Bioethanol, biodiesel, solid biofuel, biohydrogen and solid biogas are possible bioenergies, that can be produced from lignocellulosic biomass. However, hemp appears to have suitable abilities to be considered for biomass production.

As current research shows that industrial hemp combines nearly the same glucan and xylan levels in comparison with kenaf, and sorghum, which is certainly used for biomass production [31]. Also, the availability of fermentable sugars in hemp is comparable to the compared feedstocks. Accounted for, depending on the biomass type, 10-30% of the biomass together with cellulose, hemicellulose and other minor components and further one of the building blocks of plant cell walls, Lignin is another important factor in terms of bioenergy production from growths [64]. Moreover, Lignin can be converted to aromatic compounds for fuels and chemicals. It also presents a possibility in terms of making platform chemicals to improve profitability from a bio-refinery standpoint. Not only relatively low lignin levels and high amounts are reasonable abilities of hemp [11,21,31,43, 44,64-69]. Drought, microbial resistance, high biomass yield, no requirements for herbicides, almost half the requirements for nutrients in comparison with maize, the ability to grow on greatly contaminated soil, suppression of soil-borne pathogens and usage for crop rotation make hemp ultimate as a bioenergy resource [21,31,70-76].

Moreover, sugar yield analysis and enzymatic hydrolysis show that industrial hemp yields higher levels of glucose and xylose compared to kenaf and sorghum, under the same pretreatment conditions. Since the enzymatic saccharification to breakdown solid cellulose cell walls into sugars, is an important part in the process of deriving bioethanol from lignocellulosic, hemp again exhibits as a biomass source.

Biofuels have traditionally been produced based on starchy or sugar crops such as corn, wheat, sugar beets, and sugar cane. Nonetheless, industrial hemp is currently one of the top feedstocks and has great potential to become a promising commodity crop for producing biofuels and other value-added products. From an economical stand of point, industrial hemp could produce higher per hectare gross profit than other crops [31,77].

7.1 Process

Converting lignocellulosic biomass into biofuels usually includes three steps [78]. First, Pretreatment to open the rigid structure of plant cell walls. Lignocellulose Biomass, such as industrial hemp, has a diverse composition and due to interaction between fractions is its structure very complex. Lignin itself acts as a support to the cell structure. It hinders the susceptibility to microbial attack during the following hydrolysis process, in which the polysaccharides cellulose and hemicellulose are hydrolyzed to simple sugars. To make biomass more accessible for digestion, pretreatment aims to break the lignin layer. Withal, helping to decrease the crystallinity of cellulose and to increase the porosity is another purpose of the pretreatment. There are both physical and chemical, as well as thermal and biological pretreatment [15].

Second, Enzymatic saccharification to breakdown solid cellulose into sugars (hydrolysis). The enzymatic saccharification process aims to transform the carbohydrates polymers, cellulose and hemicellulose, into free monomeric sugars, break lipids down to long-chain fatty acids and split proteins into amino acids [11]. Also, is it the rate-limiting process towards the techno-economic feasibility of lignocellulosic bio-ethanol.

Due to many structural features, the enzymatic decomposition is extremely complicated and very recalcitrant.

There are two main ways to carry out the saccharification procedure. Either with

enzymatically (biological) by (hemi) cellulolytic enzymes or chemically (acidic) by sulfuric or other acids. The chemical reaction is done by using either dilute or concentrated acid. However, the high incubation time for carbohydrates degradation, the price of the enzyme, prevent of enzyme activity in the attendance of phenolic compounds and thermal inactivation of cellulase and hemicellulose enzyme are considerable issues connected with the enzymatic saccharification [66].

Third, Fermentation to produce biofuels or chemicals such as ethanol. Ethanol can be produced while traditional fermenting yeast (S. cerevisiae) produce ethanol from hexoses, recent genetic engineering has produced microorganisms that ferment pentoses in addition to hexoses into ethanol while traditional fermenting yeast (S. cerevisiae) produce ethanol from hexoses. However, most recently is the fermentation with microorganisms. They do not only ferment hexoses but also pentose, into ethanol [67,79,80].

8. VARIETY OF BIOENERGY PRODUCED BY HEMP

Bioethanol, as an alternative for petroleum-based gases, has a positive environmental impact, since it reduces greenhouse gases, and its production has considerable economic benefits. There are already feedstocks for bioethanol production. The feedstocks, which must be rich in sugar, are usually sugarcane, crops, wheat or grasses. However, Hemp biomass has emerged as the newest possibility. It is inexpensive and contains higher cellulose and lower lignin level. Due to a report from Moxley et al, hemp has a 96% glucose recovery from hemp hurds [31,43, 44,81-83]. In the U.S. hemp research in these areas has stalled due to the complexity of law [12,13,38,39].

8.1 Biohydrogen

An almost three times higher energy yield than some fossil fuels and low impact combustion products make biohydrogen highly interesting as a bioenergy resource, respectively. Incidentally, hemp has relatively low H_2 yields. Nevertheless, further investigations will unveil the factual potential of hemp for hydrogen production and hemp still is a promising feedstock [84,85].

8.2 Biodiesel

Biodiesel can be utilized for transportation fuel and power production without any modification. Besides, biodiesel is a renewable energy option and can supersede hydrocarbon-based fuels. Biodiesel consists of monoalkyl esters of long-chain fatty acids which are extracted from several renewable lipid feedstocks. The extraction includes transesterifying, employing chemical conditions to yield biodiesel. alkali, acid, enzyme and heterogeneous catalysts are used for the transesterification.

Factors like reaction temperature, catalyst, alcohol to oil ratio, agitation speed and content of free fatty acids influence the biodiesel production [86,87].

Because biodiesel production from edible oils is not sustainable, industrial hemp and its seeds is a promising, renewable and sustainable feedstock. Hempseeds have many fatty acids and high contents of accessible oil [51]. Investigations further confirmed the usability of industrial hemp for biodiesel production [88]. With a conversion efficiency of hemp seed oil to hemp oil biodiesel, from over 99.5 % and a biodiesel yield about 97%, industrial hemp has comparable traits to meet ASTM 6751-09 standards.

8.3 Biogas

Biogas is already made out of a wide variety of resources, such as animal waste, sewage sludge, crop residue or household organic waste [68,89]. However, there is barely practical research about the actual potential of industrial Hemp as a biogas feedstock [9]. Still, there is a lot of theoretical research about its potential. Seemingly, hemp offers an extensively good opportunity for biogas production. Hemp is subjected to methane production through anaerobic digestion.

In comparison with a usual crop used for biomass production, maize, hemp has a higher yield of biomass. It also produces high biogas yields, but the same amount of methane yield/ha as maize does. Yet, hemp has higher carbohydrate contents and a lower amount of lignin. These abilities make hemp ideal for biogas production. Nonetheless, hemp produces lower levels of methane since the partial conversion of carbohydrates, in comparison with maize. However, industrial hemp contains more carbohydrates and that is why the differences in the biogas yields cannot be associated with their composition. Nonetheless, carbohydrates are crucial for anaerobic digestion. Potential biomass

energy yield (PBEY) can be calculated for all crops using the HHV (Higher Heating Value) of biomass.

HHV= 0.3491(C) + 1.1783(H) + 0.1005(S) + 0.1034(O) + 0.0151(N) + 0.021(A)

[C = Carbon; H = Hydrogen; S = Sulfur; O = Oxygen; N = Nitrogen and A = Ash (all mass percentage of dry material)] [90,91].

8.4 Influences to the Biogas Production from Industrial Hemp

Harvesting influences the biogas yield of industrial Hemp. Late harvesting, from September to October is the best option, respectively. Hamp has shown a biogas yield of 290 Ndm^3/kg volatile solids, and with a biomass yield of 14.4 t/ha [93].

Further, retreatment is required, since mechanical pretreatment removes some of the structural resistance and thus results in 21% increase on biogas yield [94].

9. MEDICAL USE OF CANNABIS

Medical Cannabis, or more precisely medical marihuana, was already cultivated and used in the ancient times, due to its pharmaceutical properties and intoxicating effects [94,95,96]. However, medical marihuana, known for its high amounts of tetra hydro cannabinol, which is responsible for the intoxicating effect and the so-called "high-feeling", was prohibited by the Us Comprehensive Drug Abuse Prevention and Control Act of 1970 in the United States of America [94]. The ban included cannabis of any sort, respectively. Nonetheless, the discovery of a system of endogenous cannabinoid receptors and ligands has created interest in the therapeutic potential of Cannabis once more. Nowadays, almost 30 states in the Us [94] and countries all over the world allow at least the research or use of cannabis for medical or industrial purposes [32,97,98].

9.1 Medical

Incidentally, Cannabis with its cannabinoids has a lot of therapeutic properties. These biological properties are caused by interactions between the cannabinoids and the receptors of the endocannabinoid system in the human body. The endocannabinoid system is described in the section afterwards [16,43,84,92]. Most commonly used for pharmaceutical reasons, is the fluorescence and the leaves of the marihuana plant since these include the highest amounts of available THC and CBD [21, 94].

Nonetheless, the most important cannabinoids for medical purposes are not only THC and CBD, but also the decarboxylated forms of cannabinolic acid (CBNA), followed by cannabigerolic acid (CBGA), cannabichromenic acid (CBCA) and cannabinodiolic acid (CBNDA) [16].

The psychoactive THC is an agonist of both CB1 and CB2 receptors in the endocannabinoid system. Still, it has a higher affinity for the CB1 receptor, which seemingly mediates its psychoactive properties. Due to the variety of location of CB1 receptors, THC can also unfold their properties in the immune cells and the gastrointestinal, reproductive, adrenal, heart, lung and bladder tissues [39]. Further THC has molecular targets. THC has anti-inflammatory and anti-cancer properties and operates analgesic, muscle relaxant, neuro-antioxidative, antispasmodic, and nitride production in macrophages [97,98,99].

CBDA is the most prevalent and versatile phytocannabinoid for that matter of fact. It is also the second most important phytocannabinoid in drug chemotypes. Together with its decarboxylated form CBD it has Analgesic, antibacterial, antidiabetic, antiemetic, antiepileptic, anti-inflammatory, antiproliferative, antipsychotic, antispasmodic, antibiotic, neuroprotective and anxiolytic properties [2,3,14, 15,77,100-105].

Besides, CBD can reduce the side effects of THC and may increase the safety of Cannabis-based extracts [106]. Interestingly, these cannabinoids also possess the potential of controlling chronic pain, alleviating nausea and vomiting associated with chemotherapy, treating glaucoma and wasting syndrome associated with AIDS, controlling muscle spasms due to multiple sclerosis, Tourette's syndrome, amyotrophic lateral sclerosis, Crohn disease, epilepsy, seizures, posttraumatic stress disorder, cholinergic-mediated contractility and epilepsy and incontinence episodes of patients with multiple sclerosis [77,100-108].

Studies on mice showed that CBD has the therapeutic ability to reduce inflammatory bowel

disease (IBD) such as ulcerative colitis (UC), and Duchenne muscular dystrophy (DMD) [109-111]. CBD may be useful for treating bladder dysfunction [112]. It is also reported that CBD), cannabidivarin (CBDV) and tetrahydrocannabidivarin (THCV), can reduce inflammation and restore functional autophagy and positively enhance muscle function in vivo [113].

Also, CBD has therapeutic agents in the central modulation of feeding behaviour, has antibacterial properties and a powerful activity against methicillin-resistant Staphylococcus aureus [114]. For that matter of fact, CBDA and CBD turn out to be the most versatile source for medical purpose.

Besides the fact, that CBC is a potent inhibitor of anandamide uptake, an endogenous ligand of CB receptors, it has similar properties as CBD, such as anti-inflammatory, sedative, analgesic, anti-bacterial and antifungal properties [105,106, 115,116].

CBN is usually found in aged Cannabis and for that matter a degradation product of THC. It affects cells of the immune system more than the central nervous system since it has, it has a twofold lower a└nity for CB1 receptors and a threefold higher a└nity for the CB2 receptors, in comparison with THC [101].

9.2 Endocannabinoid System in the Human Body

The endocannabinoid system is a complex network of receptors, especially two coupled G proteins namely type 1 cannabinoid receptor (CB1) and type 2 cannabinoid receptor(CB2), ion channels (TRPV1, TRPA1, etc.), enzymes, (for instant FAAH Fatty acid amid hydrolase), carrier proteins for admitting the endocannabinoids and endocannabinoids itself [69], namely N-archidonylethanolamine (Anandamid/AEA) and 2-Arachidonoylglycerol/2-AG [58,117-119].

The endocannabinoid system is disseminated in the human body and affects numerous physiological processes such as appetite, pain-sensation, mood, memory, inflammation, insulin, sensitivity and energy metabolism and muscle disorders. The CB1 receptor is mostly located in the central nervous system and the intestinal nervous system. The CB2 receptors are in general situated on cells of the defence system of the human body and on cells which regulate the bone metabolism [65,97,119,120].

The CB1 receptor is found in the central nervous system. It is mostly located on neurons concentrated in the prefrontal cortex, basal ganglia, hippocampus, amygdala, hypothalamus and cerebellum. Further, the receptors are found in smooth muscle, myocardium, adipocytes and preganglionic sympathetic neurons integrated with the autonomic and endocrine system. The neuropsychiatric effects of cannabis, "high feeling" etc., are generated by the signals of retrosynaptic gamma-aminobutyric acid [121, 122].

Same as the CB1 receptor, the CB2 receptor can also be found in smooth muscle, but also in peripheral blood mononuclear cells such as macrophages, natural killer cells [102] and B-cells and vascular endothelium. The CB2 receptors are hypothesized to regulate neuroinflammatory response in the mesenchymal derived central nervous system microglia [6,9, 117].

Endocannabinoids are cannabinoids which appear naturally in the human body. They are synthesized by the human body but only when it is necessary. Therefore, they are also called `short term neurotransmitters´. Besides, they are degraded by the enzymes, such as FAAH or MAGL, shortly after release. N-arachidonylethanolamine and 2-arachidonoylglycero are very well-investigated endocannabinoids. 2-arachidonoylglycero exists in high levels in the brain, whereas N-arachidonylethanolamine is primary being located in other parts of the human body. They are both agonists at CB1 and CB2 receptors [123,124]. The consumption of exogen cannabinoids such as THC or CBD enhances the productivity of the endocannabinoid system.

THC with its intoxicant effect on the human body bonds with the CB1 and CB2 receptors in the same way as endocannabinoids. It has psychotropic effects but also operates on pain, nausea, appetite, asthma and glaucoma. Further, it may help in the process of curing cancer.

In comparison with THC, CBD does not have psychological but physiological effects on the human body. CBD does not bond on receptors but obstructs the production of FAAH, thus, the destruction of anandamide gets delayed. As a result, the endocannabinoid can work more effectively in the human brain [123].

9.3 Risk of Abuse and Health Risks

Overdose in cannabis consumption is associated with several side effects, that can cause serious physiological and psychological damage in the human body. Respiratory disease, psychosis and lower birth weight offspring are considered as the most dangerous. It is necessary, however, to distinguish between the effects of the ingredients of whatever cannabis- product one may consume and the way of consumption. Whereas the consumption itself is in most cases rather not dangerous, often even healthy, facing the numerous therapeutic advantages of cannabinoids.

Nonetheless, overconsumption may cause serious damage.

Psychosis is a considerable side effect of overconsumption. In contrast to CBD which has antipsychotic effects, THC with its psychotic effects is suspected to have the potential of causing schizophrenia, schizoaffective, schizophreniform and other psychotic disorders. Further, paranoia, delusions, hallucinations or disturbances in mood may appear, depending on the consumed sort of Cannabis.

Short term effects of cannabis can include confusion, sleepiness, impaired ability to remember, concentrate or pay attention, coordinate, react, ability to judge distance or making decisions, also anxiety, fear and panic can appear. Long term consumption can even influence the IQ, memory and may cause bronchitis, lung infection and increased mucus buildup in the throat or chronic long-term cough [125,126,127,128].

10. CONCLUSION

This review of *Cannabis Sativa*, also known as hemp, shows that hemp has been cultivated and used over 2,000 years, due to its medical, hallucinogenic and agricultural properties. Hemp can be considered one of the oldest crops and still can be considered as a billion-dollar plant worldwide as it has been described in 1938 by the Popular Mechanics magazine [1].

Hemp has seen as new push in recent years worldwide and the U.S. with the introduction of the 2018 Farm Bill which allows on a federal level to grow hemp, pending on individual state regulations.

The current focus on hemp beside industrial applications in the U.S. is for medical and pharmaceutical applications. Solvent extraction processes are used to extract Δ9-tetrahydrocannabinol and cannabinoids from the leaves and fluorescence of the hemp plant that contain no more than of up to 0.3% of these compounds.

The use of hemp plants with higher levels are strictly forbidden in most countries.

Nonetheless, overconsumption of cannabis products can be associated with several side effects, that can cause serious physiological and psychological damage in the human body may cause serious damage.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hartsel JA, Eades J, Hickory B, Makriyannis A. Chapter 53-cannabis sativa and hemp nutraceuticals, efficacy, safety and toxicity. Academic Press. 2016;735-754.
2. Popp JR, Petrakis EA, Angelis A, Halabalaki M, Bonn GK, Stuppner H, Skaltsounis LA. Rapid isolation of acidic cannabinoids from *Cannabis sativa* L.

using pH-zone refining centrifugal partition chromatography. Journal of Chromatography. 2019;1599:196-202.

3. Brighenti V, Pellati F, Steinbach M, Maran D, Benvenuti S. Development of a new extraction technique and HPLC method for the analysis of non-psychoactive cannabinoids in fibre type *Cannabis sativa* L (hemp). Journal of Pharmaceutical and Biomedical Analysis. 2017;143:228-236.
4. Δ9-tetrahydrocannabinol (Δ9-THC), Wikipedia, Common Domain; 2019.
   Available:https://upload.wikimedia.org/wikipedia/commons/d/d1/THC.svg
5. Leiman K, Colomo L, Armenta S, de la Guardia M, Esteve-Turrillas FA. Fast extraction of cannabinoids in marijuana samples by using hard-cap espresso machines. Talanta. 2018;190:321-326.
6. Devi V, Khanam S. Comparative study of different extraction processes for hemp (*Cannabis sativa*) seed oil considering physical, chemical and industrial-scale economic aspects. Journal of Cleaner Production. 2019;207:645-657.
7. Hemp, wikipedia, The Variety of Appearance of Cannabis, Common Domain; 2019.
   Available:https://en.wikipedia.org/wiki/Hemp#/media/File:Cannab2_new.png
8. Hanf, Wikipedia, Common Domain; 2019.
   (Accessed 18 August, 2019)
   Available:https://de.wikipedia.org/wiki/Hanf#/media/Datei:Hanfpflanze,_industriell_IMG_5412-2.jpg
9. Kitrytė V, Bagdonaitė D, Venskutonis PR. Biorefining of industrial hemo (*Cannabis sativa* L.) threshing residues into cannabinoid and antioxidant fractions by supercritical carbon dioxide, pressurized liquid and enzyme- assisted extractions. Food Chemistry. 2018;267:420-429.
10. Harper JK, Collins A, Kime L, Roth GW, Industrial hemp production, The Pennsylvania State University; 2018.
    (Accessed 8 August 2019)
    Available:https://extension.psu.edu/industrial-hemp-production
11. Karuppiah T, Azariah VE. Biomass pretreatment for enhancement of biogas production. Intertech Open. 2019;1-22.
12. Farm Bill; 2018.
    (Accessed 6 August, 2019)
    Available:https://www.agriculture.senate.gov/2018-farm-bill
13. National Conference of Legislatures, State Industrial Hemp Status; 2019.
    (Accessed 18 September, 2019)
    Available:http://www.ncsl.org/research/agriculture-and-rural-development/state-industrial-hemp-statutes.aspx
14. Rovetto LJ, Aieta NV. Supercritical carbon dioxide extraction of cannabinoids from *Cannabis sativa* L., The Journal of Supercritical Fluids. 2017;129:16-27.
15. Koeberle A, Werz O. Perspective of microsomal prostaglandin E2 synthase-1 as drug target in inflammation-related disorders. Biochemical Pharmacology. 2015;98(1):1-15.
16. ElSohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Science. 2005;78:539–548.
17. Thomas BF, ElSohly MA. Chapter 3-medical cannabis formulations. The Analytical Chemistry of Cannabis. 2016;43-61.
18. Popp JR, Petrakis EA, Angelis A, Halabalaki M, Bonn GK, Stuppner H, Skaltsounis LA. Rapid Isolation of acidic cannabinoids from *cannabis sativa* L. using pH-zone-refining centrifugal partition chromatography. Journal of Chromatography. 2019;1599:196-202.
19. Chang CW, Yen CC, Wu MS, Hsu MC, Wu YT. Microwave-assisted extraction of cannabinoids in hemp nut using response surface methodology: Optimization and comparative study. Molecules. 2017; 22(1894):1-15.
20. Sausserde R, Adamovics A. Industrial hemp for biomass production. Journal of Agricultural Engineering. 2013;XLIV(S2): e123:619-622.
21. Rehman MSU, Rashid N, Saif A, Mahmood T, Han JI. Potential of bioenergy production from industrial hemp (*cannabis sativa*). Renewable and Sustainable Energy Reviews. 2013;18:154-164.
22. Agbor V, Zurzolo F, Blunt W, Dartiailh C, Cicek N, sparling R, Levin DB. Single-step fermentation of agricultural hemp residues for hydrogen and ethanol production. Biomass and Bioenergy. 2014;64:62-69.
23. Upton R, Craker L, ElSohly M, Ronn E, Russo E, Sexton M. Cannabis

inflorescence: Standards of identity, analysis, and quality control. Scott, American Herbal Pharmacopoia, Cannabis Infloresence and Leaf. 2013;1-15.

24. Brenneisen R. Chapter 2 - Chemistry and analysis of phytocannabinoids and other Cannabis constituents Marijuana and the Cannabinoids. Springer. 2007;17–49.
25. Radwan MM, ElSohly MA, Slade D, Ahmed SA, El-Alfy WAT, Khan IA, Ross SA. Non-cannabinoid constituents from a high potency *Cannabis sativa* variety. Phytochemistry. 2008;69(14):2627–2633.
26. ElSohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Science. 2005;78(5):539–548.
27. Callaway JC, 2004. Hempseed as a nutritional resource: An overview. Euphytica. 2004;140(1–2):65–72.
28. Turner CE, Elsohly MA, Boeren EG. Constituents of *Cannabis sativa* L. XVII. A review of the natural constituents. J. Nat. Prod. 1980;43(2):169–234.
29. Turner CE, Elsohly MA, Boeren EG. Constituents of *Cannabis sativa* L. XVII. A review of the natural constituents, Journal Natural Products. 1980;43(2):169–234.
30. Thomas BF, ElSohly MA. Chapter 3- medical cannabis formulations. The Analytical Chemistry of Cannabis. 2016; 43-61.
31. Das L, Liu E, Saeed A, Williams DW, Hu H, Li C, Ray AE, Shi J. Industrial hemp as a potential bioenergy crop in comparison with kenaf, switchgrass and biomass sorghum. Bioresource Technology. 2017; 244:641-649.
32. Di Marzo V, Piscitelli F. The endocannabinoid system and its modulation by Phytocannabinoids. Neurotherapeutics. 2015;12:692–698.
33. Zule J, Černič M, Šuštaršič M. Hemp fibers for production of speciality paper and board grades; 2012.
    (Accessed August 12, 2019)
    Available:https://www.gzs.si/Portals/183/vsebine/dokumenti/2012/13-janja-zule-hemp-fibers-for-production-of-speciality-paper.pdf
34. Van Roekel GJ. Hemp pulp and paper production. Journal of the International Hemp Association. 1994;1:12-14.
35. Angelini LG, Tavarini S, Di Candilo M. Performance of new and traditional fiber hemp (*Cannabis sativa* L.) cultivars for novel applications: Stem, bark and core yield and chemical composition. Journal of Natural Fibers. 2016;13:2:238-252.
36. Small E, Marcus D. Tetrahydrocannabinol levels in hemp (*Cannabis sativa*) germplasm resources. Econ. Bot. 2003; 57(4):545–558.
37. Cappelletto P, Brizzi M, Mongardini F, Barberi B, Nenci G, Poli M, Corsi G, Grassi G, Pasini P. Italy-grown hemp: Yield, composition and cannabinoid content. Industrial Crops and Products. 2001; 13(2):101–113.
38. National Conference of State Legislatures, State Industrial Hemp Status; 2019.
39. Federal register. Statement of Principles on Industrial Hemp; 2019.
    (Accessed 12 September, 2019)
    Available:https://www.federalregister.gov/documents/2016/08/12/2016-19146/statement-of-principles-on-industrial hemp?utm_campaign=pi+subscription+mailing+list&utm_medium=email&utm_source=federalregister.gov
40. René Goscinny; 2019.
    (Accessed 16 August, 2019)
    Available:https://en.wikipedia.org/wiki/Ren%C3%A9_Goscinny
41. Albert Uderzo; 2019.
    (Accessed 16 August, 2019)
    Available:https://en.wikipedia.org/wiki/Albert_Uderzo
42. Humbold. Unterschiede zwischen Hanf und Marihuana: Morphologie, Verwendung und chemische Zusammensetzung; 2019. (Accessed 10 August 2019)
    Available:https://www.humboldtseeds.net/de/blog/19873/
43. Andre CM, Hausman JF, Guerriero G. *Cannabis sativa*: The plant of the thousand and one molecules, Frontiers in Plant Sceince. 2016;7:1-17.
44. Prade T, Svensson SE, Andersson A, Mattsson JE. Biomass and energy yield of industrial hemp grown for biogas and solid fuel. Biomass and Bioenergy. 2011; 35:3040-3049.
45. Liua M, Fernandob D, Danielb G, Madsenc B, Meyera AS, Alea MT, Thygesena A. Effect of harvest time and field retting duration on the chemical composition, morphology and mechanical properties of

hemp fibers. Industrial Crops and Products. 2015;69:29-39.

46. Watson DP, Clarke RC. The genetic future of hemp. Int. Hemp, International Hemp Association; 2014.
(Accessed 10 August, 2019)
Available:http://www.hempworld.com/hempcyberfarm_com/htms/research_orgzs/iha/ihagenetic.html

47. Vonapartis E, Aubin MP, Seguin P, Mustafa AF, Charron JB. Seed composition of ten industrial hemp cultivars approved for production in Canada. Journal of Food Composition and Analysis. 2015;39:8-12.

48. Bower JL. Industrial Hemp (*Cannabis sativa* L.) as a papermaking raw material in minnesota: Technical, Economic and Environmental Considerations. 2004;1-44.

49. How Products are Made, How industrial hemp is made - production process, making, history, used, processing, parts, components, steps; 2019.
(Accessed 8 August 2019)
Available:http://www.madehow.com/Volume-6/Industrial-Hemp.html.

50. Gesundheit. Alleskönner Cannabis: Kosmetik aus Hanf; 2019.
(Accessed 28 August, 2019)
Available:https://www.myweedo.de/gruene-seiten/gesundheit/hanf-kosmetik/, German

51. Kriese U, Schumann E, Weber WE, Beyer M, Brühl L, Matthäus B. Oil content, tocopherol composition and fatty acids patterns of the seeds of 51 *Cannabis sativa* L. genotypes. Euphytica. 2004; 137:339-351.

52. Jolie, Canabis is the new beauty wonder weapon. German; 2005.
(Accessed 28 August, 2019)
Available:https://www.jolie.de/beauty/cannabis-beauty

53. Malachowska M, Przybysz M, Dubowik M, Kucner M, Buzala K. Comparison of papermaking potential of wood and hemp cellulose pulps, Annals of Warsaw University of Life Sciences – SGGW, Forestry and Wood Technology. 2015;91: 134-137.

54. Prade T, Industrial Hemp (Cannabis sativa L.) – a High-Yielding Energy Crop, Diss. (sammanfattning/summary) Alnarp, Sweden: Sveriges lantbruksuniv. Acta Universitatis Agricultura; 2011.

55. The Boston Hemp Co-Op's Digital Hemp History Library and Museum; 2016. (Accessed 22 August 2019)
Available: http://www.hempology.org/

56. Hemp Products, Images by Klaus Dölle & David E. Kurzmann.

57. CBD Oil Production Process, Image by Klaus Dölle & David E. Kurzmann.

58. Tatke P, Jaiswal Y. An overview of microwave assisted extraction and its applications in herbal drug research. Research Journal of Medical Plants. 2011; 5:21–31.

59. Eskilsson CS, Björklund E. Analytical-scale microwave-assisted extraction. Journal of Chromatography. 2000;902:227–250.

60. Pico Y. Chapter 4 - Green Extraction Techniques, Comprehensive Analytical Chemistry; 2017.

61. Aladic K, Jarni K, Barbir T, Vidovic S, Vladic J, Bilic M, Jokic S. Supercritical CO_2 extraction of hemp (*Cannabis sativa* L.) seed oil, Industrial Crop and Products. 2015;76:472-478.

62. Banos R, Manzano-Agugliaro F, Montoya FG, Gil C, Alcayde A, Gomez J. Optimization methods applied to renewable and sustainable energy: A review, Renewable & Sustainable Energy Reviews. 2011;15:3207-3219.

63. Shi J, Qing Q, Zhang T, Wyman CE, Lloyd TA. Chapter 26 - Biofuels from cellulosic biomass via aqueous processing, fundamentals of materials for energy and environmental sustainability. Cambridge University Press. 2011;336–349.

64. Kikas T, Tutt M, Raud M, Alaru M, Lauk R, Olt J. Basis of energy crop selection for biofuel production: Cellulose vs. lignin. International Journal of Green Energy. 2016;13(1):49-54.

65. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals, Therapeutic Advances in Psychopharmacology. 2012;2(6):241-254.

66. Madadi M, Tu Y, Abbas A. Recent status on enzymatic saccharification of lignocellulosic biomass for bioethanol production. Electronic Journal of Biology. 2017;13(2):153-143.

67. Anker Y, Nakonechny F, Niazov B, Lugovskoy S, Nisnevitch M. Biofuel

Production by Fermentation of Water Plants and Agricultural Lignocellulosic by-Products. 2016;70:1-5.

68. Dölle K, Wagmüller F, Determination of the Chemical Oxygen Demand (COD) of hydrothermal pretreated hay. British Journal of Applied Science & Technology. 2015;8(4):356-360.
69. Mechoulam R, Hanus L. A historical overview of chemical research on cannabinoids. Chemistry and Physics of Lipids. 2000;108:1-13.
70. Pakarinen A, Maijala P, Stoddard F, Santanen A, Kymäläinen M, Viikari L. Evaluation of annual bioenergy crops in the boreal zone for biogas and ethanol production. Biomass and Bioenergy. 2011; 35(8):3071-3078.
71. Casas XA, Pons JR. Environmental analysis of the energy use of hemp—analysis of the comparative life cycle: Diesel vs. hemp-diesel. International Journal of Agricultural Resources, Governance and Ecology. 2005;4:133-139.
72. Struik PC, Amaducci S, Bullard MJ, Stuterheim NC, Venturi G, Cromack KTH. Agronomy of fibre hemp (*Cannabis sativa* L) in Europe. Industrial Crops and Products. 2000;11:107-118.
73. Sipos B, Kreuger E, Svensson S-E, Reczey K, Bjornsson L, Zacchi G. Steam pretreatment of dry and ensiled industrial hemp for ethanol production. Biomass and Bioenergy. 2010;34:1721-1731.
74. Shi G, Cai Q. Cadmium tolerance and accumulation in eight potential energy crops. Biotechnology Advances. 2009; 27:555-561.
75. Kok CJ, Coenen GCM, De Heij A. The effect of fibre hemp (*Cannabis sativa* L) on selected soil-borne pathogens. Journal of the International Hemp Association. 1994; 1:6-9.
76. Van der Werf HMG, Van Geel WCA, Wijlhuizen M. Agronomic research on hemp (*Cannabis sativa* L) in the Netherlands 1987-1993. Journal of the International Hemp Association. 1995; 2:14-7.
77. Walsh Z, Callaway R, ,Belle-Isle L, Capler R, Kay R, Lucas P, Holtzman S. Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. International Journal of Drug Policy. 2013;24:511-516.
78. Kamireddy SR, Li J, Abbina S, Berti M, Tucker M, Ji Y. Converting forage sorghum and sunn hemp into biofuels through dilute acid pretreatment. Industrial Crops and Products. 2013;49:598–609.
79. Dien BS, Cotta MA, Jeffries TW. Bacteria engineered for fuel ethanol production: Current status. Applied Microbiology Biotechnology. 2003;63:258-266.
80. Wooley R, Ruth M, Glassner D, Sheehan J. Process design and costing of bioethanol technology: A tool for determining the status and direction of research and development. Biotechnology Progress. 1999;15:794-803.
81. Moxley G, Zhu Z, Zhang YP. Efficient sugar release by the cellulose solvent based lignocellulose fractionation technology and enzymatic cellulose hydrolysis. Journal of Agricultural and Food Chemistry. 2008;56:7885-90.
82. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids asnoveltherapeutic agents in CNS disorders. Pharmacology Therapeutics. 2012;133:79–97.
83. Kamireddy SR, Li J, Abbina S, Berti M, Tucker M, Ji Y. Converting forage sorghum and sunn hemp into biofuels through dilute acid pretreatment. Industrial Crops and Products. 2013;49:598–609.
84. Prade T, Svensson SE, Andersson A, Mattsson JE. Biomass and energy yield of industrial hemp grown for biogas and solid fuel. Biomass and Bioenergy. 2011; 35:3040–9.
85. Almarsdottir AR, Tarazewicz A, Gunnarsson I, Orlygsson J. Hydrogen production from sugars and complex biomass by Clostridium species, AK14 isolated from Icelandic hot spring. Islandic Agricultural Sciences. 2010;23:61-71.
86. Demirbas A. Biodiesel fuels from vegetable oils via catalytic and noncatalytic supercritical alcohol transesterification and other methods: A survey. Energy Conversion and Management. 2003; 44:2093-2109.
87. Deshpande A, Anitescu G, Rice PA, Tavlarides LL. Supercritical biodiesel production and power cogeneration: Technical and economic feasibilities.

Bioresource Technology. 2010;102:1834-43.

88. Li SY, Stuart JD, Li Y, Parnas RS. The feasibility of converting *Cannabis sativa* L. oil into biodiesel. Bioresource Technology. 2010;101:8457-8460.
89. Oliveira F, Doelle K. Anaerobic digestion of food waste to produce biogas: A comparison of bioreactors to increase methane content – A review. Journal Food Process Technoloy. 2015;6(8):478:1-3.
DOI:10.4172/2157-7110.1000478
90. Channiwala SA, Parikh PP. A unified correlation for estimating HHV of solid, liquid and gaseous fuels. Fuel. 2002; 81:1051-1063.
91. Kreuger E, Escobar F, Svensoon S-E, Björnsson L. Biogas production from hemp-evaluation of the effect of harvest time on methane yield, 11th IWA World Congress on Anaerobic Digestion. Brisbane, Australia; 2007.
92. Prade T, Svensson SE, Andersson A, Mattsson JE. Biomass and energy yield of industrial hemp grown for biogas and solid fuel. Biomass and Bioenergy. 2011; 35:3040–9.
93. Pakarinen A, Maijala P, Stoddard F, Santanen A, Kymäläinen M, Viikari L. Evaluation of annual bioenergy crops in the boreal zone for biogas and ethanol production. Biomass and Bioenergy. 2011; 35(8):3071-3078.
94. Ebbert JO, Scharf EL, Hurt RT. Medical Cannabis. Mayo Clinic Proceedings. 2018; 93(12):1842-1847.
95. Russo EB, Jiang HE, Li X, Sutton A, Carboni A, delBianco F, Mandolino G, Zhao YX, Bera S, Zhang TB, Lü EG, Ferguson DK, Hueber F, Zhao LC, Liu CJ, Li CS. Phytochemical and genetic analyses of ancient Cannabis from central. Asia. J. Exp. Bot. 2008;59:4171–4182.
96. Skoglund G, Nockert M, Holst B. Viking and early Middle Ages northern Scandinavian textiles proven to be made with hemp. Scientific Reports. 2013; 3:2686.
97. De Petrocellis L, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Britisch Journal of Pharmacology. 2011; 163:1479–1494.
98. Arbeitsgemeinschaft Canabis als Medizin e.V. Cannabissorten und ihre THC- und CBD-Gehalte; 2019.
(Accessed 8 August 2019)
Available:https://www.arbeitsgemeinschaft-cannabis-medizin.de/impressum/- German
99. Romano B, Pagano E, Orlando P, Capasso R, Cascio MG, Pertwee R, Marzo VD, Izzo AA, Borrelli F. Pure Δ(9)-tetrahydrocannabivarin and a Cannabis sativa extract with high content in Δ(9)-tetrahydrocannabivarin inhibit nitrite production in murine peritoneal macrophages. Pharmacol Res. 2016; 113(Pt A):199-208.
100. Amar BM. Cannabinoids in medicine: A review of their therapeutic potential, Journal of Ethnopharmamacology. 2006; 105:1-25.
101. McPartland JM, Russo EM. Cannabis and cannabis extracts: Greater than the sum of their parts? Journal of Cannabis Therapeutics. 2001;3-4:103-132.
102. Baker D, Pryce P, Giovannoni G, Thompson AJ. The therapeutic potential of cannabis. Lancet Neuro. 2013;2:291-298.
103. Hollister L. An approach to the medical marijuana controversy. Drug Alcohol Dependence. 2003;58:3-7.
104. Belendiuk KA, Baldini LL, Bonn-Miller MO. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-proved medical and psychiatric disorders. Addiction Science & Clinical Practice. 2015;10(10):1-10.
105. Davis WM, Hatoum NS. Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol, General Pharmacology: The Vascular System. 1983;14:247–252.
106. Englund AM, Stone J, Morrison PD. Cannabis in the arm: What can we learn from intravenous cannabinoid studies? Current Pharmaceutical Design. 2012; 18:4906–4914.
107. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids asnoveltherapeuticagents in CNS disorders, Pharmacology Therapeutics. 2012;133:79–97.
108. Capasso R, Aviello G, Borrelli F, Romano B, Ferro M, Castaldo L, Montanaro V, Altieri V, Izzo AA. Inhibitory effect of standardized cannabis sativa extract and its ingredient cannabidiol on rat and

human bladder contractility. Urology. 2011;77(4):1006.e9-e15.

109. Pagano E, Capasso R, Piscitelli F, Romano B, Parisi OA, Finizio S, Lauritano A, Marzo VD, Izzo AA, Borrelli F. An orally active cannabis extract with high content in cannabidiol attenuates chemically-induced intestinal inflammation and hypermotility in the mouse. Front Pharmacol. 2016;7:341.
110. Borrelli F, Fasolino I, Romano B, Capasso R, Maiello F, Coppola D, Orlando P, Battista G, Pagano E, Di Marzo V, Izzo AA. Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. Biochem Pharmacol. 2013;85(9):1306-1316.
111. Pagano E, Romano B, Iannotti FA, Parisi OA, D'Armiento M, Pignatiello S, Coretti L, Lucafò M, Venneri T, Stocco G, Lembo F, Orlando P, Capasso R, Di Marzo V, Izzo AA, Borrelli F. The non-euphoric phytocannabinoid cannabidivarin counteracts intestinal inflammation in mice and cytokine expression in biopsies from UC pediatric patients. Pharmacol Res. 2019;104464:1-12.
112. Pagano E, Montanaro V, Di Girolamo A, Pistone A, Altieri V, Zjawiony JK, Izzo AA, Capasso R. Effect of non-psychotropic plant-derived cannabinoids on bladder contractility: Focus on cannabigerol. Nat Prod Commun. 2015;10(6):1009-1012.
113. Iannotti FA, Pagano E, Moriello AS, Alvino FG, Sorrentino NC, D'Orsi L, Gazzerro E, Capasso R, De Leonibus E, De Petrocellis L, Di Marzo V. Effects of non-euphoric plant cannabinoids on muscle quality and performance of dystrophic mdx mice. Br J Pharmacol. 2019;176(10):1568-1584.
114. Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M, Antibacterial cannabinoids from *Cannabis sativa*: A structure-activity study. J. Nat. Prod. 2008; 71:1427–1430.
115. DeLong GT, Wolf CE, Poklis A, Lichtman AH. Pharmacological evaluation of the natural constituent of Cannabis sativa, cannabichromene and its modulation by 9-tetrahydrocannabinol. Drug and Alcohol Dependence. 2012;112:126–133.
116. Eisohly HN, Turner CE, Clark AM, Eisohly MA. Synthesisand antimicrobial activities of certain cannabichromene and cannabigerol related compounds. Journal of Pharmaceutical Science. 1982;71: 1319–1323.
117. Ester F. Das endogene Cannabinoidsystem: Ein neuer Akteur in der Gehirn Darm Fett Achse, Cannabinoids. German. 2007;2(2):6-16.
118. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocrine Review. 2006;27(1):73-100.
119. Cannabidiol (CBD) Und der Einsatz im Sport Canna Sport Research.; German; 2017.
(Accessed 8 August, 2019)
Available:https://www.cannasport-research.com/german/was-ist-das-endocannabinoisystem/
120. Iannotti FA, Pagano E, Guardiola O, Adinolfi S, Saccone V, Consalvi S, Piscitelli F, Gazzerro E, Busetto G, Carrella D, Capasso R, Puri PL, Minchiotti G, Di Marzo V. Genetic and pharmacological regulation of the endocannabinoid CB1 receptor in Duchenne muscular dystrophy. Natural Commun. 2018;9(1):3950.
121. Hoehe MR, Caenazzo L, Martinez MM, Hsieh WT, Modi WS, Greshon ES, Bonner TI. Genetic and physical mapping of the human cannabinoid receptor gene to chromosome 6ql4-ql5. New Biology. 1991; 3(9):880-885.
122. Gerard C, Mollereau C, Vassart G, Parmentier M. Nucleotide sequence of a human cannabinoid receptor cDNA, Nucleic Acids Research. 1990; 18(23):7142.
123. What is the endocannabinoid system and how does it work? Royal Queen Seeds German; 2017.
(Accessed 6 August, 2019)
Available:https://www.royalqueenseeds.de/content/140-zum-verstandnis-des-endocannabinoid-systems
124. Ranieri R, Marasco D, Bifulco M, Malfitano AM. Phytocannabinoids and cannabimimetic drugs: Recent patents in central nervous system disorder. Recent Pat CNS Drug Discov. 2016;I0(2):3-19.
125. Leirer VO, Yesavage JA, Morrow DG. Marijuana carry-over effects on aircraft pilot performance. Aviat. Space Environ. Med. 1991;62:221–227.

126. Karschner EL, Swortwood MJ, Hirvonen J, Goodwin RS, Bosket WM, Ramaekers JG, Huestis MA. Extended plasma cannabinoid excretion in chronic frequent cannabis smokers during sustained abstinence and correlation with psychomotor performance. Drug Testing and Analysis. 2016; 8(7):682–689.

127. Meier H, Caspi A, Ambler A, Harrington HL, Houts R, Keefe RSE, McDonald K, Ward A, Poulton R, Moffitt TE, Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences USA. 2012;109(40):2657–2664.

128. Bhattacharyya S, Morison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O' Carroll CM, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PA. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuro Psycho Pharmacology. 2010;35(3):764–774.

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